

REMARKSRegarding the Claim Amendments presented in this reply:

The amendments to claim 1 add no new matter. These amendments find support in the specification on page 10, line 16 (with regard to “cohesive”), and in the specification on page 11, lines 15 – 16 (with regard to “multi-screw extruder”). The other amendments to claim 1 are cosmetic in nature.

New claims 10 – 20 add no new matter. These claims find support in the original specification.

- New claim 10 finds support on page 12, lines 6 – 10.
- New claim 11 finds support on page 10, lines 23 – 29.
- New claim 12 finds support on page 10, lines 23 – 29.
- New claim 13 finds support on page 10, lines 23 – 29.
- New claim 14 finds support on page 10, lines 31 – 35.
- New claim 15 finds support on page 10, line 35 – page 11, line 1.
- New claim 16 finds support on page 11, lines 9 – 12.
- New claim 17 finds support on page 11, lines 9 – 12.
- New claim 18 finds support on page 11, lines 32 – 37.
- New claim 19 finds support on page 11, line 32 – page 12, line 1.
- New claim 20 finds support on page 12, lines 2 – 4.

Regarding the Claimed Invention:

The embodiment of the invention claimed in independent claim 1 relates to a process for producing solid dosage forms, comprising forming a moldable cohesive composition by heating at a temperature at or above the softening point of the adjuvant, but at least 70°C, in a multi-screw extruder and subsequently cooling the moldable composition. The moldable cohesive composition must comprise a) 50 to 99.4% by weight of at least one crosslinked nonthermoplastic carrier, b) 0.5 to 30% by weight of at least one adjuvant selected from the group consisting of thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers and c) 0.1 to 49.5% by weight of at least one active ingredient.

The process of the present invention yields a cohesive moldable composition which solidifies to a hard brittle mass. The compositions of the present invention

disintegrate in water within a few minutes (*See examples 1, 2, 5, 6 and 7*).

Regarding the Claim Rejection:

Claims 1 – 9 stand rejected under 35 U.S.C §103(a) over *Vladyka et al.* (US 2002/0012706 A1) in view of *Thacharodi et al.* (EP 0960 620 A1).

The *Vladyka et al.* Reference

Vladyka discloses “methods and formulations for improving the aqueous solubility of crystalline pharmaceutical compounds having low water solubility”¹ Vladyka explains that “[m]any crystalline, pharmaceutical compounds have very slight solubility in aqueous fluids such as those found in the human body.”² The Vladyka reference is directed toward providing “improved solubility and bioavailability of a sparingly water-soluble, crystalline pharmaceutically active agent, such as itraconazole.”³ The reference results in:

a granular formulation in which the granular particles comprise a solid solution of an amorphous pharmaceutically active agent which is normally crystalline and sparingly water-soluble at ambient temperature and pressure, dissolved in a molten solution of a pharmaceutically acceptable normally solid hydrophobic vehicle in which the active agent is soluble at elevated temperature; a stabilizing agent to stabilize the active agent in its amorphous state; a disintegrant; and optionally a binder, wherein the dissolved active agent is substantially stabilized in an amorphous state as a solid solution in said granular particles.⁴

Vladyka makes clear that “significant improvement in bioavailability ... requires

¹ Paragoroh [0001] of US 2002/0012706 A1.

² Paragoroh [0002] of US 2002/0012706 A1.

³ Paragoroh [0011] of US 2002/0012706 A1.

⁴ Paragoroh [0012] of US 2002/0012706 A1 (emphasis added).

that the resulting solution of the active ingredient be stable.”⁵ Vladyka stresses that “it is believed that the entire formulation and the interaction of its components is required for the stabilization to occur to the extent that has been observed. Accordingly, the granular particle of this invention may comprise … about 3% to about 25% of the disintegrant, preferably croscarmellose”⁶ In other words, Vladyka teaches that using more than about 25% of the disintegrant would disrupt the stability of the resulting solid solution. Such a loss in stability would render the Vladyka invention unsuitable for its intended purpose. As explained by Vladyka, “[w]ithout this stabilization, crystallization and precipitation of the dissolved active agent may occur, thereby reducing the bioavailability of the active agent that has not yet been absorbed into the patient’s bloodstream.”⁷ It is important to note that the Vladyka reference is directed toward providing “improved solubility and bioavailability of a [a particular class of active ingredient, i.e., a] sparingly water-soluble, crystalline pharmaceutically active agent, such as itraconazole.”⁸

Clearly, Vladyka contains a strong teaching away from using more than about 25% of the disclosed disintegrant. This teaching away is so strong, in fact, that a skilled artisan would have concluded that using more than about 25% of the disclosed disintegrant would render the Vladyka invention unsuitable for its intended purpose, i.e., providing a stable solution of a particular class of active ingredient to improve bioavailability.

Again, Vladyka discloses a method of making a granular pharmaceutical vehicle. Vladyka provides no teaching, suggestion, motivation, or apparent reason that would have prompted a skilled artisan to redesign the Vladyka process so as to form a moldable cohesive composition. Indeed, Vladyka teach away from making any such modification, by touting the benefits of the resulting granular particles. More specifically, the reference explains, “[t]he resulting granular particles may … be milled to an appropriate particle size, and filled into capsules, or blended with other excipients and processed into solid dosage forms.

Applicants also note that the compositions of Vladyka provide a dissolution of

⁵ Paragoroh [0010] of US 2002/0012706 A1 (emphasis added).

⁶ Paragraph [0026] of US 2002/0012706 A1 (emphasis added).

⁷ Paragoroh [0010] of US 2002/0012706 A1.

⁸ Paragoroh [0011] of US 2002/0012706 A1.

87% after 30 minutes and 94% after one hour (see example 6 of Vladyka).

The *Thacharodi et al.* Reference

Thacharodi discloses a pharmaceutical composition which comprises a specific active ingredient (substituted pyridylsulfinyl benzimidazole, such as omeprazole). The reference explains that “[d]rugs in this class are known to be highly unstable in an acidic environment. They are also unstable in the presence of moisture and organic solvents. Thus, the formulation in which the drugs are to be administered to a patient, and the process for manufacture of the formulation, must be designed to protect the drug from moisture as well as an acidic environment.”⁹ To this end, the Thacharodi pharmaceutical composition further comprises a carrier which acts as a stabilizing excipient. The carrier comprises at least one polymer having vinyl pyrrolidone monomeric units.

According to Thacharodi, useful polymers are polyvinylpyrrolidones¹⁰, crosslinked polyvinylpyrrolidone¹¹ and water soluble vinylpyrrolidone-vinylacetate copolymers.¹² Thacharodi makes no distinction between crosslinked polyvinylpyrrolidone, non-crosslinked polyvinylpyrrolidone, and vinylpyrrolidone copolymers.

The Proposed Combination

A skilled artisan would not have chosen the crosslinked polyvinylpyrrolidone out of the polymers described in Thacharodi to be employed in the hot granulation process of Vladyka. Applicants respectfully submit that the selection of crosslinked polyvinylpyrrolidone from Thacharodi is based on an unfair hindsight bias. Again, Thacharodi makes no distinction between crosslinked polyvinylpyrrolidone, non-crosslinked polyvinylpyrrolidone, and vinylpyrrolidone copolymers. A skilled artisan had no apparent reason to select crosslinked polyvinylpyrrolidone over the other

⁹ Paragraph [0002] of EP 0 960 620 A1 (emphasis added).

¹⁰ See page 4, line 42 of EP 0 960 620 A1.

¹¹ See page 4, line 51 of EP 0 960 620 A1.

¹² See page 4, line 58 to page 5, line 1 of EP 0 960 620 A1.

polymers. This is especially true because it is generally known by persons of ordinary skilled in the art that crosslinked polyvinylpyrrolidone cannot be molten without decomposition. Thus, a skilled artisan would not have chosen the crosslinked polyvinylpyrrolidone out of the polymers described in Thacharodi to be employed in the hot granulation process of Vladyka.

Moreover, Thacharodi discloses a pharmaceutical composition which comprises a specific active ingredient known to be highly unstable in an acidic environment, and unstable in the presence of moisture and organic solvents.¹³ The Thacharodi carrier acts as a stabilizing excipient and is designed to protect the drug from moisture as well as an acidic environment.¹⁴ On the other hand, Vladyka is directed toward providing “improved solubility and bioavailability of a sparingly water-soluble, crystalline pharmaceutically active agent, such as itraconazole.”¹⁵ These divergent purposes must not be overlooked when evaluating whether the proposed combination would have been obvious to a person of ordinary skill in the art at the time the invention was made.

Applicants respectfully submit that the Office action does not adequately explain why a skilled artisan would have combined two references designed to achieve diametrically opposed purposes. The Office action states that a skilled artisan would have used a high percentage (10 to 98%) of cross-linked polyvinylpyrrolidone in the Vladyka process, merely because Example 6 of Thacharodi uses 66.67% of Kollidon CL-M in a stable oral pharmaceutical composition.¹⁶ Applicants respectfully submit that a skilled artisan would have appreciated that the Thacharodi carrier acts as a stabilizing excipient and is designed to protect a specific drug, known to be highly unstable in an acidic environment, and unstable in the presence of moisture and organic solvents from moisture as well as an acidic environment. Therefore, the teaching of Example 6 of Thacharodi, does not provide any apparent reason to modify the Vladyka process which is directed toward providing “improved solubility and bioavailability of a sparingly water-soluble, crystalline pharmaceutically active agent, such as itraconazole.”¹⁷

Moreover, Applicants respectfully submit that the Office action improperly avoids

¹³ See Paragraph [0002] of EP 0 960 620 A1.

¹⁴ See Paragraph [0002] of EP 0 960 620 A1.

¹⁵ Paragoroh [0011] of US 2002/0012706 A1.

¹⁶ See Page 5, lines 10 – 20 of the Office action mailed December 05, 2007.

¹⁷ Paragoroh [0011] of US 2002/0012706 A1.

consideration of Vladyka's strong teaching away from modifying the disclosed weight percentage of disintegrant. Again, Vladyka teaches away from using more than about 25% of the disclosed disintegrant. Based on this teaching away, a skilled artisan would have concluded that using more than about 25% of the disclosed disintegrant would render the Vladyka invention unsuitable for its intended purpose, i.e., providing a stable solution of a particular class of active ingredient to improve bioavailability.

Claim 1, as amended, requires the use of a multiscrew extruder. It is believed that the use of the extruder combines a short exposition of the components to elevated temperatures with sufficient mixing action and shear force input to yield the compositions of the present invention having unique properties. Neither Vladyka nor Thacharodi teach or suggest the use of a multiscrew extruder.

Finally, claim 1, as amended, requires the formation of a moldable cohesive composition. Vladyka discloses a method of making a granular pharmaceutical vehicle. Vladyka provides no teaching, suggestion, motivation, or apparent reason that would have prompted a skilled artisan to redesign the Vladyka process so as to form a moldable cohesive composition. Indeed, Vladyka teach away from making any such modification, by touting the benefits of the resulting granular particles. More specifically, the reference explains, “[t]he resulting granular particles may ... be milled to an appropriate particle size, and filled into capsules, or blended with other excipients and processed into solid dosage forms. Similarly, Thacharodi states [d]esirably, the composition is in the form of a simple powder blend or granules of the active ingredient and the carrier, together with any optionally included excipients filled into an enteric capsule....”¹⁸ Thus, the proposed combination would not result in a moldable cohesive composition.

¹⁸ Paragraph [0011] of EP 0 960 620 A1.

In Conclusion:

The present application is in condition for allowance. Applicants request favorable action in this matter. In order to facilitate the resolution of any issues or questions presented by this paper, the Examiner is welcome to contact the undersigned by phone to further the discussion.

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Respectfully submitted,
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